RHEUMATOLOGY

Letter to the Editor

Rheumatology 2011;50:243–244
doi:10.1093/rheumatology/keq258
Advance Access publication 17 August 2010

Do new biologics meet the unmet medical need in rheumatoid arthritis? Safety and efficacy of abatacept following B-cell depletion

Sir, anti TNF-α agents (aTNFs) are the most commonly prescribed biological agents in RA. More recently abatacept (ABA), a T-cell costimulation modulator, and rituximab (RTX), a monoclonal antibody directed against CD20, have become available. Observational studies suggest that switching to a new drug class may be more effective in uncontrolled RA than switching to a class of biologics to which the patient had unsuccessfully been exposed [1]. Information about the efficacy and safety of cycling strategies through third-line biologics is lacking. This study aimed to analyse the effectiveness and safety of switching patients to ABA as the third biological class after failure of aTNF plus RTX.

The Swiss Clinical Quality Management (SCQM) programme for RA is a longitudinal population-based cohort, which has been approved by the local ethics committees of all participating centres [2]. For this analysis, we collected all the cases of RA with an inadequate response to at least one aTNF plus RTX, followed by ABA. As our programme is mainly aimed at efficacy data, an additional chart review for severe adverse events (SAEs) was performed in all cases. We analysed the evolution of 28-joint DAS (DAS-28) using mixed linear models for longitudinal data [3].

By March 2009, 28 of 5056 SCQM patients met the inclusion criteria. Patients had an average of 6.3 assessments during a median follow-up of 22.1 months [interquartile range (IQR) 17.4–31.3 months]. All patients discontinued RTX because of insufficient disease control. The key demographic, disease- and treatment-related characteristics of patients are provided in Table 1.

The mean DAS-28 did not improve significantly over time (mean improvement at 6 months 0.38 DAS units, $P = 0.48$). Only six ABA patients (21%) had a clinically meaningful DAS-28 improvement (0.6 units) after 6 months. However, the mean daily prednisone dose was 2.1 mg lower compared with baseline ($P = 0.01$). ABA was discontinued in 16 patients after a median drug retention of 10.1 months (IQR 4.3–12.0 months). ABA was discontinued within the first 6 months in eight patients (six due to lack of improvement or clinical worsening, one due to liver enzyme elevation and one due to the patient's desire).

SAEs during ABA included pneumonia (two patients), erysipelas with bursitis, shingles, urinary tract infection requiring antibiotics and rash (one patient each), yielding an AE rate of 2.83/100 patient-years. The patient with erysipelas was admitted for antibiotics. There was no opportunistic infection and no permanent damage.

Table 1 Demographic and disease characteristics of RA patients at the time of switch from RTX to ABA

Patient and RA characteristics	
n	28
Female, *n* (%)	20 (71.4)
Age, mean (s.d.), years	61.2 (11.4)
DAS-28 at switch from RTX, mean (s.d.)	4.7 (2.5)
RA duration, mean (s.d.), years	13.2 (9.2)
RF positive, %	71.4
CCP positive, %	78.6
Number of biologics before RTX, mean	1.8
Months between RTX and ABA, mean (s.d.)	11.7 (7.0)
Patients on glucocorticosteroids, %	77.8
Prednisone equivalent, mean (s.d.), mg	8.3 (5.8)
Concomitant DMARD treatment	
MTX or leflunomide, %	20 (83.3)
Other non-biologic DMARDs, %	2 (8.3)
No DMARDs, %	6 (21.4)

Meta-analyses of randomized placebo-controlled trials do not suggest an increased risk of serious infections with RTX or ABA in comparison with placebo when given either as first biologic, or after aTNF [4]. These meta-analyses were, however, underpowered and also unable to provide information of an added risk of previous biological treatment. In RA patients on treatment with biological agents, the addition of ABA was associated with an increase in serious infections [5]. Genovese *et al*. [6] have previously collected safety but not efficacy data of patients treated with biological agents following RTX, 25 of whom received ABA. In this analysis, the rate of serious infectious events did not increase with the new biologic agent compared with before exposure.

Our analysis is clearly limited by its observational nature and the small sample size. Nevertheless, our data set represents the largest analysis so far of patients with ABA after RTX. Our data add to the existing safety data but suggest that the efficacy of ABA as a third-line biologic is limited after failure of aTNF plus RTX. Thus, failure in response to aTNF and RTX identifies a difficult-to-treat RA population whose needs are currently not met and should become a focus of clinical trials.

Rheumatology key message

- RA patients respond poorly to abatacept as the third class of biological agents.

LETTER

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source: https://doi.org/10.7892/boris.1640 | downloaded: 5.5.2023

Acknowledgements

We are grateful to the rheumatologists and patients participating in the SCQM, who made this study possible.

Funding: This work was supported by a grant from Hoffmann La Roche, Basel to partially cover the costs of D.S.C. and A.S. for this project. Roche had no role in the design of the study, interpretation of data or the writing of the manuscript.

Disclosure statement: A.F. has received consultancies or honoraria from Abbott, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer and Roche. U.A.W. has received speaker's honoraria from Hoffmann La Roche and BMS. J.vK. has received honoraria from BMS. All other authors have declared no conflicts of interest.

Ulrich A. Walker[1], Delphine S. Courvoisier[2], Jean Dudler[3], Daniel Aeberli[4], Johannes von Kempis[5], Almut Scherer[6] and Axel Finckh[7] on behalf of the Swiss Clinical Quality Management Programme in Rheumatic Diseases

[1]Division of Rheumatology, University Hospital of Basel, Basel, [2]Division of Clinical Epidemiology, University of Geneva, Geneva, [3]Division of Rheumatology, University Hospital of Lausanne, Lausanne, [4]Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Bern, Bern, [5]Division of Rheumatology and Rehabilitation, Kantonsspital, St Gallen, [6]Swiss Clinical Quality Management Foundation, Zurich and [7]Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland

Accepted 6 July 2010
Correspondence to: Ulrich A. Walker, Department of Rheumatology, University of Basel, Basel, Switzerland.
E-mail: ulrich.walker@fps-basel.ch

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